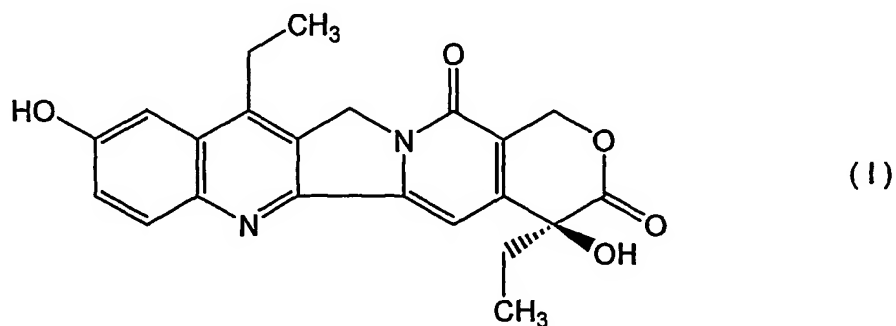


AP3 Rec'd PCT/PTO 13 JUN 2006

**The Method of Manufacturing of 7-Ethyl-10-hydroxycamptothecin****Field of the Invention**

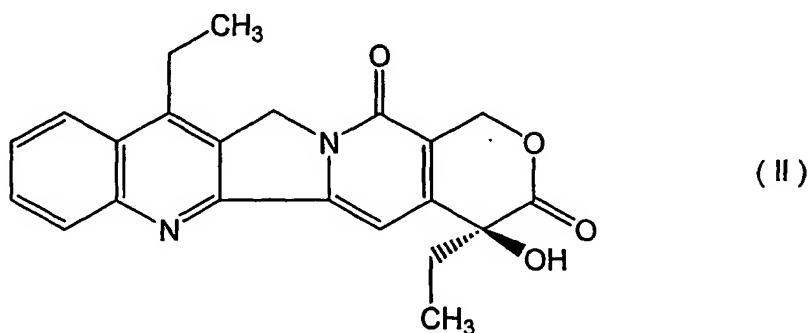
This invention relates to the method of manufacturing of 7-ethyl-10-hydroxycamptothecin of formula I



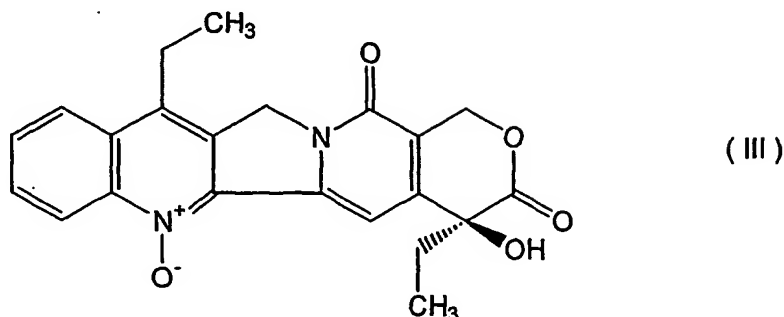
which is used for manufacturing of cytostatically active irinotecan hydrochloride trihydrate, effective particularly in treatment of lung and rectum cancer. The cytostatic effect of irinotecan hydrochloride trihydrate is based on its ability to inhibit topoisomerase.

**Background of the Invention**

So far, 7-ethyl-10-hydroxycamptothecin is usually prepared in two reaction steps. In the first reaction step, 7-ethylcamptothecin of formula II



is oxidized with hydrogen peroxide in acetic acid under formation of 7-ethylcamptothecin 1-oxide of formula III



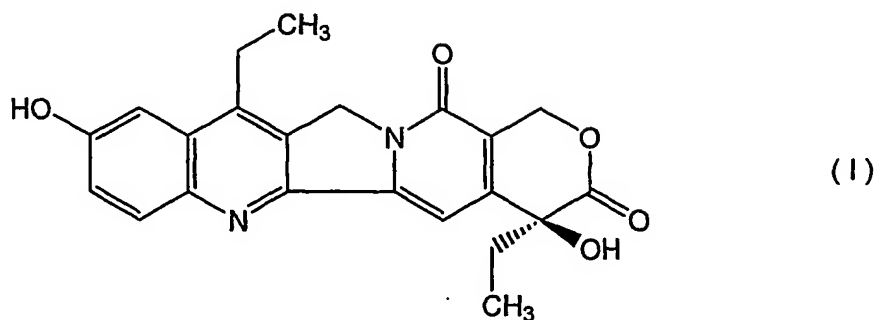
which in the second reaction step is dissolved in the solvent system dioxane-acetonitrile-water and the solution is irradiated with UV light in the presence of sulfuric acid to afford the desired 7-ethyl-10-hydroxycamptothecin (see US 4 473 692 and US 4 513 138 and Zhongguo Yaowu Huaxue Zazhi 2001, 11 (4), 238-240).

However, this method of manufacturing of 7-ethyl-10-hydroxycamptothecin suffers from the fact that the oxidation of 7-ethylcamptothecin in the first reaction step requires relatively great amount of acetic acid (300 ml of acetic acid per 1 gram of 7-ethylcamptothecin). In the isolation of the obtained 7-ethylcamptothecin 1-oxide it is necessary to evaporate one fourth of the acetic acid volume, add water to the evaporation residue and subsequently collect the precipitated 7-ethylcamptothecin 1-oxide by filtration. This isolation procedure is demanding and affects very unfavourably the yield of 7-ethylcamptothecin 1-oxide. In the second step, the isolation of 7-ethyl-10-hydroxycamptothecin, consists in removal of the solvent mixture by distillation, dilution with water, extraction with chloroform and drying the chloroform layer over magnesium sulfate, followed by purification on a silica gel column with the aim to remove impurities arising in the UV irradiation. In spite of this complicated isolation procedure, the obtained 7-ethyl-10-hydroxycamptothecin still contains up to 22 % by weight of 7-ethylcamptothecin. In this method the total yield of both reaction steps is only about 38 %.

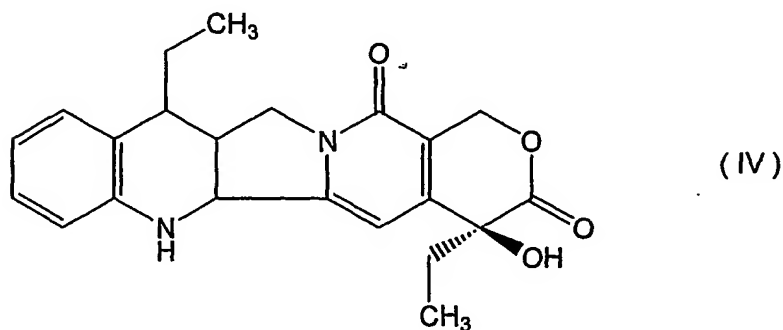
The aim of the invention is to find a less demanding method of producing 7-ethyl-10-hydroxycamptothecin that would afford 7-ethyl-10-hydroxycamptothecin in higher yields and higher purity. This aim has been achieved by the method according to the present invention.

### Summary of the Invention

The present invention relates to the method of manufacturing of 7-ethyl-10-hydroxycamptothecin of formula I

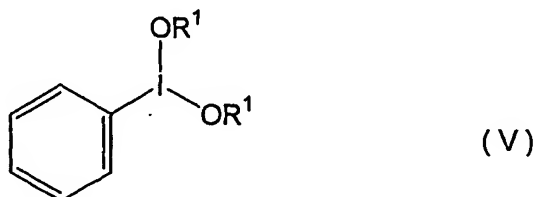


which is characterized in that 7-ethyl-1,2,6,7-tetrahydrocamptothecin of formula IV



is oxidized with an oxidizing agent selected from the group comprising iodosobenzene, an ester of iodosobenzene, sodium periodate, potassium periodate, potassium peroxodisulfate and ammonium peroxodisulfate, in the presence of a solvent formed by a saturated aliphatic monocarboxylic acid comprising 1 to 3 carbon atoms, and in the presence of water.

The oxidizing agent is preferably an ester of iodosobenzene, more preferably an ester of iodosobenzene of general formula V



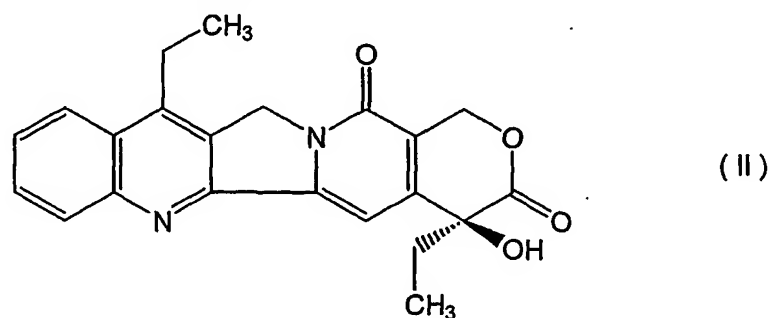
in which substituents  $R^1$  are the same or different and designate hydrogen,  $-C(O)-R^2$  or  $-SO_2-R^3$  where  $R^2$  and  $R^3$  independently are selected from a group comprising an optionally substituted alkyl group having 1 to 6 carbon atoms, an optionally substituted cycloalkyl group having 3 to 8 carbon atoms, an optionally substituted aryl group having 6 to 12 carbon atoms, and an optionally substituted aralkyl group in which the aryl moiety has 6 to 12 carbon atoms and the alkyl moiety has 1 to 4 carbon atoms, with the proviso that at least one of the substituents  $R^1$  is not the hydrogen atom, in particular an ester of iodosobenzene selected from a group comprising iodobenzene diacetate, iodobenzene bis(trifluoroacetate) and hydroxy(tosyloxy)iodobenzene. Iodobenzene diacetate is advantageously used in an amount of 0.99 to 1.85 mol, more advantageously 1.28 to 1.56 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

Suitable solvents include acetic acid, formic acid or trifluoroacetic acid. Preference is given to acetic acid in amounts from 668 to 1001 mol, more preferably 751 to 918 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

Water is advantageously used in amounts from 0.98 to 1.88 mol, preferably from 1.28 to 1.58 mol, per 1 mol of 7-ethyl-1,2,6,7-tetrahydrocamptothecin.

The oxidation is carried out preferably at a temperature in the range of 15 to 30 °C, more preferably at 18 to 25 °C, the reaction time being 5 to 30 minutes, more preferably 10 to 15 minutes.

The starting 7-ethyl-1,2,6,7-tetrahydrocamptothecin is preferably obtained by hydrogenation of 7-ethylcamptothecin of formula II



in a saturated aliphatic monocarboxylic acid having 1 to 3 carbon atoms, using hydrogen in the presence of a hydrogenation catalyst and a sulfur compound partly deactivating the hydrogenation catalyst.

Preferred saturated aliphatic monocarboxylic acids are formic acid, acetic acid or trifluoroacetic acid, more preferred being acetic acid in an amount of 791 to 1187 mol, most preferably 890 to 1088 mol, per 1 mol of 1-ethylcamptothecin.

Preferred sulfur compound that partly deactivates the hydrogenation catalyst is dimethyl sulfoxide, preferably in an amount of 0.18 to 0.33 mol, more preferably in an amount of 0.23 to 0.28 mol, per 1 mol of 7-ethylcamptothecin.

Preferred hydrogenation catalyst is a noble metal, preferably platinum which is advantageously used on a carrier consisting of an activated carbon or aluminum oxide. Platinum is advantageously used in an amount of 0.018 to 0.027 mol, more advantageously in an amount of 0.020 to 0.025 mol, per 1 mol of 7-ethylcamptothecin, in the form of hydrogenation catalyst consisting of platinum on an activated carbon with platinum content of 5 %. The hydrogenation is performed advantageously at a pressure from 0.3 to 0.7 MPa, more preferably at 0.4 to 0.6 MPa, at a temperature from 45 to 85 °C, more preferably at 58 to 72 °C, for 24 to 70 hours, more preferably for 40 to 50 hours.

After the end of the oxidation, undesired compounds are removed in the following way. The solvent is distilled off, 7-ethyl-10-hydroxycamptothecin is precipitated in acetonitrile and isolated by filtration and washing with acetonitrile. In the procedure according to the present invention, at least 58 % yield of 7-ethyl-10-hydroxycamptothecin is achieved in a relative purity of 90 %, as determined by high performance liquid chromatography.

A substantial advantage of the method according to this invention over the prior art ones is that in the oxidation of 7-ethyl-1,2,6,7-tetrahydrocamptothecin no coloured side products are formed that need be removed by chromatography on a silica gel column. In an advantageous embodiment of this invention, the oxidation is preceded by hydrogenation of 7-ethylcamptothecin under formation of 7-ethyl-1,2,6,7-tetrahydrocamptothecin which advantageously is not isolated, the oxidation being performed directly with the obtained hydrogenation mixture from which only the hydrogenation catalyst has been removed.

In the following example, the method according to this invention is described in more detail, this example being for illustration only, without limiting in any way the scope of the invention which is unequivocally defined by the patent claims and the description part.

## Examples

### Example 1

In a 100 ml beaker, 0.5 g (1.239 mmol) of 7-ethylcamptothecin, 0.32 g of 5% hydrogenation catalyst Pt/C (containing 0.028 mmol of platinum) and 0.025 ml (0.352 mmol) of dimethyl sulfoxide are added to 70 ml of acetic acid. The obtained suspension is quantitatively transferred into a 100 ml autoclave. After closure, the autoclave is flushed three times with nitrogen at the pressure of 0.5 MPa and then three times with hydrogen at the pressure of 0.5 MPa. The temperature is adjusted to 65 °C and the mixture is stirred at 950 r.p.m. The hydrogen pressure is adjusted to 0.5 MPa. After 43.5 hours the consumption of hydrogen stops and the procedure is terminated. After cooling to 25 °C, the stirring is stopped and the internal pressure is equilibrated with the ambient atmosphere. The autoclave is flushed three times with nitrogen, the hydrogenation catalyst is removed from the hydrogenation mixture by filtration under pressure of nitrogen and the catalyst cake is washed with 10 ml of acetic acid. The obtained solution (80 ml) of 7-ethyl-1,2,6,7-tetrahydrocamptothecin is immediately added under vigorous stirring into a 250 ml one-necked flask containing 22 ml (1.218 mol) of water and 0.77 g (2.343 mmol) of iodobenzene diacetate. The obtained solution is stirred for 15 minutes at 22 °C. Then the solvent is evaporated and the residue is mixed with 10 ml of acetonitrile. The obtained suspension is homogenized by sonication. The solid 7-ethyl-10-hydroxycamptothecin is isolated by filtration, washed on the filter with 10 ml of acetonitrile and dried to the constant weight in a vacuum oven at 60 °C to 65 °C. The yield of 7-ethyl-10-hydroxycamptothecin is 0.283 g (58.3 %). Its relative purity, determined by high performance liquid chromatography, is 90.2 %.